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# Cerebral white matter lesions and subjective cognitive dysfunction

## The Rotterdam Scan Study

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**Article abstract**—*Objective:* To determine the relationship between cerebral white matter lesions (WML) and subjective cognitive dysfunction. *Background:* Subjective cognitive dysfunction is present when a person perceives failures of cognitive function. When annoying enough, these failures will be expressed as complaints. Subjective cognitive dysfunction may be a prelude to or coincide with objective cognitive impairment. WML have been related to objective cognitive impairment and dementia, but their relationship with subjective cognitive dysfunction is not clear. Previous population-based studies on the latter relationship have been limited in sample size, recording of subjective cognitive function, and assessment of WML severity. *Methods:* We randomly sampled 1,049 elderly nondemented participants from the general population. Data on subjective cognitive dysfunction and its progression were derived from a 15-item questionnaire. Objective cognitive performance was assessed using a series of neuropsychological tests. WML were scored on MRI for periventricular and subcortical regions separately. *Results:* WML were associated with more subjective cognitive failures. WML were more severe for participants reporting progression of these failures compared with participants without these failures, especially within participants with better than average cognitive performance ( $p = 0.008$ , for periventricular WML). Participants with severe WML reported progression of cognitive failures more than twice as often than did those with little or no WML. The relationship between the severity of WML and subjective cognitive failures was present for periventricular and subcortical WML. *Conclusions:* WML are associated with subjective cognitive failures and in particular with reporting progression of these failures, even in the absence of objective cognitive impairment.

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In cross-sectional studies, complaints regarding memory correlate better with depressed mood<sup>1</sup> than with objective memory performance.<sup>2,3</sup> In a longitudinal population-based study of nondemented nondepressed elderly, however, memory complaints and depressive symptoms predicted a dementia syndrome 3 years later, even in people without cognitive impairment.<sup>4</sup> The above findings indicate that cognitive complaints, although subjective, may be a prelude to objective cognitive impairment or that these complaints of cognitive function are more sensitive than neuropsychological tests to detect slight failures of cognitive function. Subjective cognitive dysfunction can consist of failures (mentioned when asked for) or, when annoying enough, complaints (spontaneously mentioned).

Cerebral white matter lesions (WML) have been related to cognitive dysfunction<sup>5–7</sup> and may eventually lead to dementia.<sup>8,9</sup> Previously, a small cross-sectional population-based study showed an association between WML and subjective memory complaints among elderly people.<sup>10</sup> Based on these findings, we hypothesize that when severity of WML is only mild, subjective loss

of cognitive function could occur in the absence of detectable cognitive impairment. Increasing severity of WML would then be accompanied by progression of subjective cognitive dysfunction and by an increased detection of measurable cognitive impairment.

The aim of this study was to investigate whether the severity of periventricular or subcortical WML or both is associated with the number of subjective cognitive failures or the reported progression of these failures and whether this association depends on the presence of objective cognitive impairment. Because the presence of subjective cognitive failures could merely reflect the presence of depressive symptoms, we studied whether the association between WML and subjective cognitive failures depended on the presence of depressive symptoms.

**Methods.** *Study population.* The Rotterdam Scan Study was designed to study determinants and consequences of age-related brain changes in the elderly, and participants were recruited from two large ongoing prospective cohort studies: the Rotterdam Study and the Zoe-termeer Study. Both studies have been described in detail

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elsewhere.<sup>11,12</sup> In short, the Rotterdam Study is a population-based prospective cohort study among 7,983 elderly, aged 55 years and older at baseline (1990), and was designed to study determinants of neurologic, cardiovascular, endocrine, and ophthalmologic diseases. The Zoetermeer study is a population-based prospective cohort study among 10,361 persons, aged 5 to 91 years at baseline (1975), and was concerned with the prevalence of various chronic diseases.

Eligible participants for the Rotterdam Scan Study, being between 60 and 90 years of age, were randomly invited by strata of age (5 years) and gender in 1995 and 1996. Details concerning the selection of participants and the design of the Rotterdam Scan Study have been published previously.<sup>7,13</sup> Briefly, of the 1,904 randomly selected people, 187 had contraindications for the study (e.g., dementia, contraindications for MRI scanning, blindness), leaving 1,717 eligible subjects, of whom 1,077 (63%) completed all investigations. Responders differed from nonresponders by being younger, being more educated (5% more had a university level education,  $p = 0.05$ ), and having higher baseline Mini-Mental State Examination scores (age- and gender-adjusted mean difference 0.4 points,  $p < 0.001$ ), but equal cholesterol levels, body mass index, and blood pressure measurements.<sup>13</sup> The protocol was approved by the medical ethics committee of the Erasmus University Rotterdam, the Netherlands, and all participants gave written informed consent.

**MRI procedure.** Cranial MRI scanning was performed with 1.5-tesla scanners at two centers using acquisition sequences, as published previously.<sup>7</sup> Scans were made from the vertex to the foramen magnum with 5- or 6-mm thick slices (scanner-dependent) and an interslice gap of 20%. Hardcopies were printed with a 2.7 reduction factor.

White matter lesions were considered present if visible as hyperintense on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted images. WML were considered periventricular if the largest diameter was adjacent to the ventricular lining; otherwise, they were considered subcortical. A WML severity score was used to assess the extent of increased white matter signal intensity on proton-density weighted images for the periventricular and subcortical areas separately. Details on the scoring method have been described previously.<sup>7,13</sup> Briefly, periventricular WML were scored semiquantitatively (range, 0–3) for locations at the frontal and occipital horns and the lateral walls of the ventricles separately. These scores were added to acquire a total periventricular score (range, 0–9). For subcortical WML, an index for their total volume as appearing on hardcopy was approximated based on number and size (small, 1–3 mm; medium, 3–10 mm; or large, >10 mm) of all subcortical lesions (range, 0–29.5).

Other recorded brain features were the severity of cerebral atrophy and the presence of cerebral infarcts on MRI. Subcortical atrophy was measured by the ventricle-to-brain ratio (range, 0.21–0.45). Cortical atrophy was rated on a semiquantitative scale (range, 0–15). Cerebral infarcts were defined as hyperintense on proton density and T2-weighted images and hypointense on T1-weighted images.

All scans were examined by two readers from a pool of four experienced physicians. In the case of disagreement of

more than one point for periventricular WML or cortical atrophy scores, a consensus reading was held; in other instances, the mean of two scores was used. Intrareader and interreader studies showed a good to excellent agreement. Weighted kappas were between 0.79 and 0.90 for periventricular WML severity grades and were 0.81 for cortical atrophy. Interreader and intrareader-intraclass correlation coefficients were 0.88 and 0.95 for subcortical WML volume and 0.57 and 0.76 for subcortical atrophy.

Of all persons, only 54 (5%) had no WML at the periventricular and subcortical locations; 217 (20%) were without any sign of periventricular WML; and 81 (7.5%) were without any subcortical WML.

**Subjective and objective cognitive assessment.** A semistructured interview based on the Cognitive Failure Questionnaire<sup>14</sup> was used to obtain information on subjective cognitive function. All information was collected without the help of a surrogate. Because the information was gathered during an interview, the answers reflect subjective cognitive failures rather than complaints. The interview consisted of 15 questions regarding cognitive problems experienced the month before (table 1). Responses were added to a sum-score for subjective cognitive failures with a maximum of 25 and a sum-score for memory problems with a maximum of 14. By design, subjective failure in remembering, word finding, planning, concentration, or slowness of thought had a higher weight in the sum-scores. We additionally asked whether these subjective cognitive failures had progressed during the past 5 years (no progression, little progression, or obvious progression). Progression of such failures was defined as present when a participant reported little progression on at least two of these cognitive failures or obvious progression of at least one failure. Data on the subjective cognitive failure score (SCF) and progression of subjective cognitive failures were complete for 1,049 participants (97%). At least some subjective cognitive failures were reported by 756 (72%) participants, of whom 233 (22%) reported progression of cognitive failures during the last 5 years.

Objective cognitive performance was assessed by neuropsychological tests, including an abbreviated Stroop test consisting of three subtasks; the Paper-and-Pencil Memory Scanning Task consisting of four subtasks<sup>15,16</sup>; the Letter-Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test<sup>17</sup>; a verbal fluency test; and a 15-word verbal learning test based on Rey's auditive recall of words.<sup>18</sup> Performance across tests was made comparable by transforming the raw test scores into standardized Z-scores as described elsewhere.<sup>19</sup> As an overall measure of cognitive performance, we used a compound score, referred to as the Cognitive Index, which was calculated as the mean of the Z-scores on the one-letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test, the Letter-Digit Substitution Task, the added score on the learning trials of the 15-word verbal learning test, and the delayed recall of this last test.<sup>7</sup> According to tertiles of the Cognitive Index distribution, we categorized cognitive performance as poor, average, or good.

**Other measurements.** The following characteristics were considered as possible confounding variables: age, gender, level of education (according to UNESCO),<sup>20</sup> and mood disturbances as determined by the Center of Epide-

miologic Studies on Depression Scale (CES-D).<sup>21</sup> Additional neuroimaging findings considered as potential confounding variables in the relationship between WML and subjective cognitive failures or cognitive function were cerebral atrophy and the presence of infarcts.

**Statistical analysis.** For the analyses, only subjects with complete data on the SCF were used ( $n = 1,049$ ). To estimate the influence of each individual item of the SCF scale to the overall SCF score, we calculated Spearman's correlation coefficients. Differences in SCF scores between genders were analyzed using an age-adjusted analysis of covariance. Across cognitive performance groups, differences in SCF scores were studied using analysis of covariance, and differences in reporting progression of SCF were studied using a logistic model (all adjusted for age, gender, and CES-D score). Associations between age and SCF scores were studied with gender-adjusted linear regression analysis.

Initially, all analyses of the relationship between WML and SCF were performed for periventricular and subcortical WML, separately adjusting for age and gender with additional adjustments for all possible confounding variables (level of education, CES-D score, score on the Cognitive Index, cerebral atrophy, and the presence of infarcts). Furthermore, we studied the relationship between periventricular WML and subjective cognitive failure conditional on subcortical WML and vice versa, by entering periventricular and subcortical WML simultaneously in the statistical model.

The relationship between WML severity and SCF scores was studied by two different approaches. First, the mean WML severity of participants with and without subjective cognitive failures was calculated, taking the reported progression of subjective cognitive failure into account using analysis of covariance. To investigate whether the level of objective cognitive performance modified this association, these analyses were additionally performed in strata of the Cognitive Index. Second, we studied whether an increased WML severity was associated with a higher SCF score (using analysis of covariance), with WML severity (in quintiles) as the independent variable and SCF score as the dependent variable. For the test for trend over these quintiles of WML severity, we used linear regression analysis and adjusted for the same variables as in the analysis of covariance.

The association between WML severity in quintiles and the reported progression of subjective cognitive failures was studied using a logistic model. To investigate whether the level of actual cognitive performance modified the relationship between WML severity and the reported progression of subjective cognitive failures, dummy variables were constructed for all 15 combinations of quintiles of WML severity and tertiles of the Cognitive Index. These dummy variables were used as independent variables in the logistic model using subjects with a good cognitive function in the lowest quintile of WML severity as the reference category.

**Results.** Of all subjects, only 28% were free of subjective cognitive failures. Table 1 lists the item-specific SCF frequency and correlation to the total of SCF score. The mean correlation of the items to the sum-score was 0.40 (range, 0.15–0.75; see table 1). The correlation of the SCF score with the Cognitive Index was lower ( $R = -0.19$ ,  $p < 0.001$ )

than with the CES-D score ( $R = 0.34$ ,  $p < 0.001$ ). Table 2 lists the general characteristics of the study population. On average, women had higher SCF scores than did men (age adjusted difference = 0.7,  $p = 0.002$ ). This gender difference remained when the analyses were corrected for educational level and cognitive performance but disap-

**Table 1** Subjective Cognitive Failures Questionnaire

Question	Score range	% With problems*	R (ir)†
Memory problems			
Do you consider yourself as forgetful?	0–3	41.0	0.75
Do you experience word-finding problems?	0–3	34.5	0.67
Do you ever forget names of family members or friends?	0–1	22.0	0.48
Do people tell you that you tell stories twice?	0–1	22.8	0.37
Do you ever forget occurrences of the past one or two days?	0–1	6.7	0.30
Do you worry about forgetfulness?	0–1	16.4	0.44
Do you experience difficulty in everyday life because of forgetfulness?	0–1	7.6	0.38
Do you ever misplace items at odd locations, leave the stove burning, or forget how to use everyday appliances?	0–1	4.4	0.22
Do you ever forget appointments?	0–1	5.9	0.27
Do you ever lose your way in your neighborhood or not recognize a person with whom you are well acquainted?	0–1	1.5	0.15
Related cognitive problems			
Have you experienced problems with planning of activities?	0–3	2.3	0.23
Do you have concentration problems?	0–3	12.2	0.45
Do you think or act more slowly than you used to?	0–3	21.4	0.51
Do you feel more exhausted than you used to?	0–1	13.5	0.39
Do you ever feel so depressed that you lose interest in life?	0–1	12.4	0.32

Scoring of items with 0–3 range: 0 = no problems; 1 = doubtful problems; 2 = moderate problems; 3 = serious problems. Scoring of items with 0–1 range: 0 = no; 1 = yes.

\* Percentage of the study population reporting problems with this item, indicating at least moderate problems on items having a score range of 0–3, or a score of 1 on dichotomous items.

† Spearman's R (ir): item score–total score correlation coefficient.



**Table 2** Characteristics of the 1,049 participants who completed the Subjective Cognitive Failure Questionnaire

Characteristic	Value
Mean age, y (SD)	72.1 (7.4)
No. (%) women	545 (52)
No. (%) people with only primary education	357 (34)
Median (range) score on the Center of Epidemiological Studies on Depression Scale (IQR)	4 (1–9)
Median (range) score on the Mini-Mental State Examination (IQR)	28 (26–29)
Subjective cognitive failures (SCF)	
No. (%) people with SCF	756 (72)
Median (range) of the sum-score on the SCF questionnaire (IQR)	2 (0–5)
No. (%) people with subjective memory failures	692 (66)
Median (range) sum-score of sub-questionnaire on memory problems (IQR)	2 (0–4)
No. (%) people reporting progression of SCF in last 5 years	232 (22)
Neuroimaging characteristics	
Median (range) volume of subcortical WML (IQR)	0.19 (0.03–1.25)
Median (range) grade of periventricular WML (IQR)	2.0 (0.5–4.0)
No. (%) people with any cerebral infarct	259 (25)
Mean (SD) grade of cortical atrophy	1.1 (0.6)
Mean (SD) ventricle-to-brain ratio	0.32 (0.04)

SD = standard deviation; IQR = interquartile range; WML = white matter lesions.

peared when CES-D scores were taken into account ( $p = 0.89$ ). The gender-adjusted SCF score was age-dependent, increasing 0.4 per 5-year increase in age ( $p < 0.001$ ). Additional adjustment for educational level, CES-D scores, and cognitive performance halved the effect estimate of this relationship (SCF score increased 0.2 per 5-year increase in age,  $p = 0.008$ ). Compared with subjects in the good cognitive performance group, subjects in the poor cognitive performance group had higher SCF scores (difference = 0.7,  $p = 0.009$ , adjusted for age, gender, and CES-D score) and were more likely to report progression of SCF (odds ratio = 1.5; 95% confidence interval [CI]: 1.0–2.3, adjusted for age, gender, and CES-D score).

Subjects who reported progression of subjective cognitive failures had the most severe periventricular WML (2.7; 95% CI 2.5 to 3.0, age and sex adjusted), followed by subjects with subjective cognitive failures who reported no progression (2.3; 95% CI 2.1 to 2.5) and subjects without subjective cognitive failures (2.2; 95% CI 2.0 to 2.4). There were no differences in subcortical WML severity between these SCF groups (all differences  $p > 0.49$ ). When stratified on cognitive performance, the above pattern was most clear in subjects with good cognitive performance (figure

1). As we reported previously,<sup>7</sup> a lower cognitive performance was related to an increase in periventricular (figure 1) and subcortical WML severity. Additional adjustment for all possible confounding variables (level of education, CES-D score, cerebral atrophy, and presence of infarcts) did not alter any of the above relationships.

As shown in figure 2, subjects with more severe WML reported more subjective cognitive complaints. The difference in (age- and gender-adjusted) SCF score was 1.1 between the lowest and highest quintile of periventricular WML (95% CI: 0.4–1.8) and 1.3 between the lowest and highest quintile of subcortical WML (95% CI: 0.6–2.0). There was a linear relationship between quintiles of periventricular WML and SCF scores (per quintile increase in WML severity, SCF score increased 0.3;  $p_{\text{trend}} < 0.001$ ) and between quintiles of subcortical WML and SCF scores (0.2;  $p_{\text{trend}} = 0.01$ ). Although interquintile differences in SCF score decreased after additional adjustment for all possible confounding variables, the linear relationships between periventricular WML and SCF scores remained (0.2;  $p_{\text{trend}} = 0.02$ ) and became less apparent for subcortical WML (0.1;  $p_{\text{trend}} = 0.07$ ). Moreover, the linear relationship between periventricular WML and SCF scores remained (0.2;  $p_{\text{trend}} = 0.01$ ), when studied conditional on the severity of subcortical WML, whereas it disappeared for subcortical WML (0.04;  $p_{\text{trend}} = 0.67$ ).

Subjects in the higher quintiles of WML severity more often reported progression of subjective cognitive failures during the last 5 years when compared with subjects in the lowest quintile (age- and gender-adjusted odds ratio for the fifth quintile of periventricular WML = 2.3 [95% CI 1.4 to 4.0] and for subcortical WML 2.6 [95% CI 1.5 to 4.5]). These relationships remained unaltered when additionally adjusted for all other possible confounding variables. Moreover, progression of subjective cognitive failures remained more frequent among subjects in the highest quintile of periventricular WML (odds ratio = 2.3; 95% CI 1.2 to 4.5), when the relationships were studied conditional on the severity of subcortical WML, whereas vice versa this was less clear for the highest quintile of subcortical WML (odds ratio = 2.0; 95% CI 1.0 to 4.1).

When we stratified subjects by level of cognitive performance (tertiles of the Cognitive Index), no relationship was found between increasing severity of subcortical WML and reporting progression of subjective cognitive failures over time in all three strata (data not shown). However, an increased severity of periventricular WML remained related to reporting progression of subjective cognitive failures in all three strata (figure 3). Among subjects with good cognitive performance, subjects in the highest quintile of periventricular WML severity reported progression of subjective cognitive failures approximately 2.5-fold more often (odds ratio = 2.3; 95% CI 0.9 to 5.9) than did subjects in the lowest quintile of periventricular WML. Subjects who had a poor cognitive performance more often reported progression of subjective cognitive failures than did subjects with an average or good cognitive performance, regardless of the severity of WML (figure 3).

**Discussion.** In this study, the severity of WML was associated with subjective cognitive dysfunction and the reported progression of such dysfunction during the last 5 years. The relationship was found

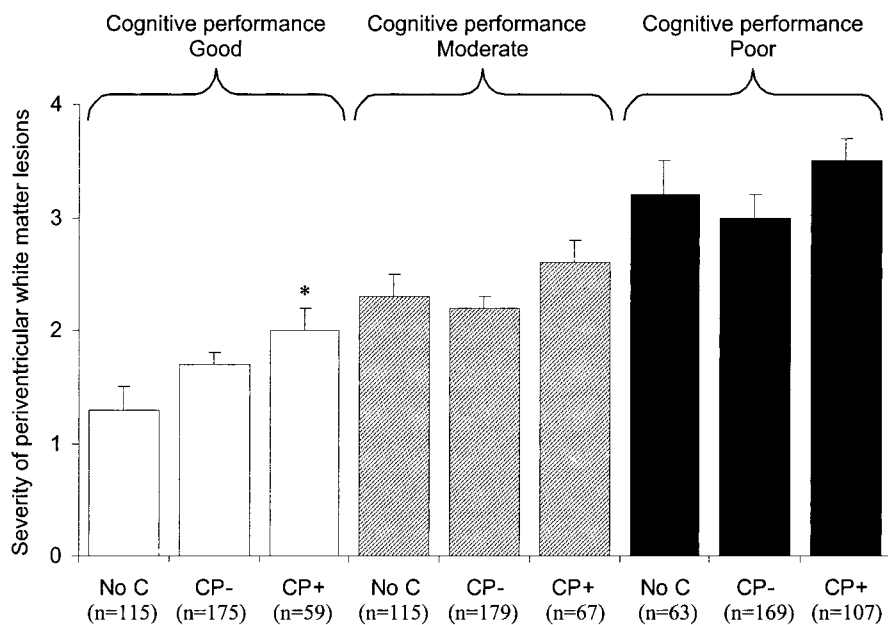


Figure 1. Age- and gender-adjusted mean severity (+SE) of white matter lesions for subjects without subjective cognitive failures, with subjective cognitive failures but without reporting progression of these, and with subjective cognitive failures who reported progression of these failures, in strata of objective cognitive performance (tertiles of the Cognitive Index). No C = subjects who reported no subjective cognitive failures; CP- = subjects who reported subjective cognitive failures but did not report progression of these failures during the last 5 years; CP+ = subjects who reported subjective cognitive failures and reported progression of these failures during the last 5 years. \*The p value for the difference between CP+ group and no C group within this stratum is 0.008.

for periventricular and subcortical WML but more consistently for periventricular WML. To our knowledge, this is the first large population-based study of the relationship between cerebral WML and subjective cognitive function.

Before we interpret these results, we must discuss the nature of our assessment of subjective cognitive dysfunction. Because we used a questionnaire for gathering information on subjective cognitive dysfunction, the data represent subjective cognitive failures. Failures are everyday mishaps in cognitive

tasks and are reported when actively asked for. They differ from complaints, in that the latter are reported spontaneously or have been the reason for seeking medical advice. The subjective cognitive problems evaluated in this study represent at least cognitive

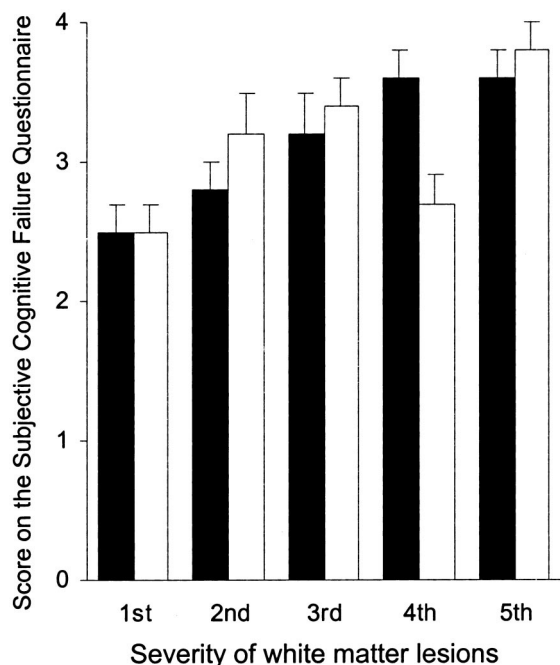


Figure 2. Score on the Subjective Cognitive Failure Questionnaire per quintile of white matter lesion severity (adjusted for age and gender [+SE]). Solid bars = periventricular; white bars = subcortical.

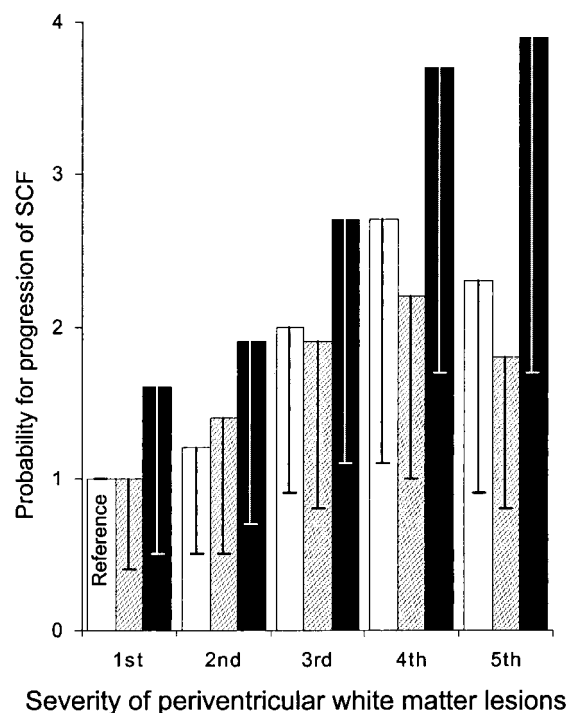


Figure 3. The relative probability for reporting progression of subjective cognitive failures (SCF) during the last 5 years per severity of periventricular white matter lesions (in quintiles) in strata of objective cognitive performance (expressed as age- and gender-adjusted odds ratios with the lower 95% confidence intervals indicated). White bars = good cognitive performance; shaded bars = moderate cognitive performance; solid bars = poor cognitive performance.

failures, but could also include cognitive complaints and is therefore a broader definition.

Previously, an association between WML and subjective memory dysfunction has been reported, although no inferences could be made as to the location of WML and no stratification was performed on objective cognitive performance.<sup>10</sup> We found more severe WML in subjects reporting subjective cognitive failures compared with subjects without such failures, especially in subjects with a better than average cognitive performance. This finding supports the hypothesis that complaints regarding cognitive function may precede measurable cognitive dysfunction<sup>22</sup> or even dementia.<sup>4</sup> In addition, we observed more severe WML in subjects who reported progression of subjective cognitive failures compared with subjects who did not report progression. This confirms an earlier report, in which memory complaints per se did not relate to memory impairment, but subjects who reported new memory complaints after 1 year of follow-up were five times more likely to have measurable cognitive impairment compared with subjects who still did not report memory problems.<sup>23</sup>

The cross-sectional association between subjective cognitive failures and indicators for depression (CES-D score) was stronger than with cognitive function. It could therefore be argued that subjective cognitive failures are a proxy for depression rather than for cognitive dysfunction. This however does not exclude subjective cognitive failures as a prelude to cognitive dysfunction. Our results are compatible with this latter hypothesis. First, we found a more robust association between subjective cognitive failures and periventricular rather than subcortical WML, whereas periventricular WML are reported to have an association with cognitive dysfunction<sup>7,24,25</sup> and subcortical WML have been related to depression.<sup>1,26,27</sup> Second, we found a stepwise increase in periventricular WML severity when we compared people with a good cognitive performance without subjective cognitive failures, with people with a good cognitive performance but with reported progression of subjective cognitive failures, and with people with a poor cognitive performance regardless of subjective cognitive failures (see figure 1). Third, independent of depressive symptoms, subjects in the poor cognitive performance group had higher SCF scores and were more likely to report progression of subjective cognitive failures than were subjects in the good cognitive performance group, as would be expected if subjective cognitive failures precede objective cognitive impairment.

Taken together, the relationship between WML severity and cognitive problems followed a sort of dose-dependent pattern. On the low end of the WML severity distribution are subjects without subjective cognitive failures with good cognitive performance, followed by subjects with subjective cognitive failures but without measurable cognitive dysfunction, and subjects who report subjective cognitive failure

progression during the last 5 years with measurable cognitive dysfunction. Our data suggest that reporting progression of subjective cognitive failures might be an early warning sign related to progression of WML and imminent cognitive decline.

Although in this study we included questions on progression of subjective cognitive failures, the study is not longitudinal. Prospective studies are needed to confirm that progression of WML severity is indeed accompanied by a progression of subjective cognitive failures and eventually to measurable cognitive impairment.

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## Presenilin-1-associated abnormalities in regional cerebral perfusion

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**Article abstract**—*Objective:* To investigate the influence of the presenilin-1 gene (*PS-1*) mutation on regional cerebral perfusion, SPECT was evaluated in 57 individuals. The subjects were members of a large pedigree from Colombia, South America, many of whom carry a *PS-1* mutation for early-onset AD. *Methods:* Members of this large kindred who were cognitively normal and did not carry the *PS-1* mutation ( $n = 23$ ) were compared with subjects who were carriers of the mutation but were asymptomatic ( $n = 18$ ) and with individuals with the mutation and a clinical diagnosis of AD ( $n = 16$ ). Cerebral perfusion was measured in each subject using hexamethylpropyleneamine oxime SPECT. The data were analyzed in two ways: 1) Mean cerebral perfusion in each of 4320 voxels in the brain was compared among the groups using *t*-tests (*t*-maps); and 2) each individual received a weighted score on 20 vectors (factors), based on a large normative sample ( $n = 200$ ), using a method known as singular value decomposition (SVD). *Results:* Based on *t*-maps, subjects with the *PS-1* mutation who were asymptomatic demonstrated reduced perfusion in comparison with the normal control subjects in the hippocampal complex, anterior and posterior cingulate, posterior parietal lobe, and anterior frontal lobe. The AD patients demonstrated decreased perfusion in the posterior parietal and superior frontal cortex in comparison with the normal control subjects. Discriminant function analysis of the vector scores derived from SVD (adjusted for age and gender) accurately discriminated 86% of the subjects in the three groups ( $p < 0.0005$ ). *Conclusion:* Regional cerebral perfusion abnormalities based on SPECT are detectable before development of the clinical symptoms of AD in carriers of the *PS-1* mutation.

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The majority of patients with AD under the age of 60 carry a mutation in the presenilin-1 gene (*PS-1*). At least 50 such mutations on the *PS-1* gene have been identified among over 80 families of various ethnic origins.<sup>1</sup> These mutations confer autosomal dominant inheritance, with virtually 100% penetrance. One of these mutations, which occurs at codon 280 in the *PS-1* gene, has been identified in a large multigenerational family living in Colombia, South America.<sup>2</sup> Individuals

with this mutation will therefore eventually develop AD, if they live through the age of risk, whether or not they are symptomatic at any one point in time. The average age at onset of AD in this kindred is 47 years.

A number of MR studies have been conducted in pedigrees with a *PS-1* mutation.<sup>3</sup> However, to our knowledge, there have been no studies of cerebral perfusion in individuals with mutations of the *PS-1* gene.

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